(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles to deposit a sub to low nanoliter volume at each location, whereby an array of material on the surface of the substrate is formed; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry.

REMARKS

A check for the fees for a three month extension of time and a Notice of Appeal accompanies this response. A Notice of Appeal is filed herewith. Any fees that may be due in connection with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

A Change of Address of the undersigned has been filed under separate cover.

Claims 1-6, 9-34, 40-51 and 54-94 are pending n this application. Claims 1, 25, 31, 40 and 70 are amended to recite that it is sub to low nanoliter volumes of fluid that are dispensed. Basis for this may be found throughout the specification. For example, at page 19, lines 10-14, the specification recites with reference to the methods described in the application:

> In another aspect, the invention provides methods for rapidly analyzing sample materials. To this end sample arrays can be formed on a substrate surface according to any of the techniques discussed above. The sample arrays are then analyzed by mass spectrometry to collect spectra data that is representative of the composition of the samples in the array.

At page 25, lines , the specification recites:

> For reproducibilty studies in different MS modes, typically a 10 x 10 array of 0.2-20 nL droplets were dispensed.

The further evidences that deposition of sub to low nanoliter volumes is intended.

Claim 5 is rewritten as an independent claims incorporating all limitations of the base claim and correcting inadvertent errors in antecedent basis. Therefore not new matter has been added. In addition, it is respectfully submitted that the amendments to the claims do not require new search or raise any new issues. The amendments find basis in the specification and address issues raised by the Examiner.

A marked up version of the amended claims pursuant to 37 C.F.R. §1.121 is appended hereto.

THE REJECTION OF CLAIMS 1-6, 9-34, 40-51, 54-69 and 70-101 UNDER 35 U.S.C. § 103(a)

Rejection over Tisone in view of Patterson

Claims 1-6, 9-34, 40-51, 54-69 and 87-93 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tisone, U.S. Patent No. 5,743,960 ("Tisone") in view of Patterson, U.S. Patent No. 5,869,240 ("Patterson") because Tisone is alleged to teach a method for dispensing a material on a substrate substantially similar to that as presently claimed. Tisone's method is alleged to comprise the steps of providing a vesicle having an interior chamber containing a fluid, disposing the vesicle adjacent to a first location on the surface of a substrate, controlling the vesicles to eject from the chamber a nanoliter volume of the fluid to dispense the fluid at the first location on the surface of the substrate, and moving the vesicle to a set of positions so that fluid is dispensed from the vesicle at each location of the set for forming an array of fluid material (figures 1, 6 and 7). Tisone is also alleged to teach that the method can be used to dispense sample fluids onto a diagnostic test strip for testing. It is acknowledged that Tisone does not teach or suggest the step of performing mass spectrometry analysis for the material. Nevertheless, it is alleged that such an analysis step is considered conventional in the art and is taught or suggested in Patterson. Patterson is alleged to teach a method for sequencing polymers using a mass spectrometer in order to provide a rapid,

automated and cost effective sequencing of polymers with a statistical certainty.

It is concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method and apparatus of Tisone with a spectrometer as taught in Patterson to provide a rapid, automated and cost effective sequencing of polymers with a statistical certainty.

The rejection is respectfully traversed insofar as it applies to any the presently pending claims. It is respectfully submitted that the instant claims are not prima facie obvious over the combination of references for reasons of record. In addition, notwithstanding the failure of the Examiner to set forth a prima facie case of obviousness, a DECLARATION under 37 C.F.R. §1.132 was previously submitted.

As discussed previously and below, the primary references cited are Tisone and Ershow, each of which teaches a reagent dispensing apparatus that dispenses small volumes. Neither reference teaches or suggests that the resulting arrays should have small spots that result from deposition of small volumes (low nanoliter volumes or less) and neither reference teaches or suggests using the resulting deposited material in mass spectrometric analyses. Patterson is cited for allegedly teaching mass spectrometry.

Patterson teaches integrated methods and apparatus for sequencing or identifying polymers by mass spectrometry with a statistical certainty. Patterson does not teach or suggest using small spots that result from delivery of nanoliter volumes (Patterson uses spots that derived from delivery of microliter volumes; see, *e.g.*, col. 11, line 567) nor that use of small spots is advantageous for mass spectrometric analyses. There is no suggestions in

Patterson or either secondary reference that spot sizes that result from deposition of low nanoliter volumes or less would be advantageous for analysis by mass spectrometry. The volumes used by Patterson are in the microliter range, and there is no motivation or suggestion provided by any reference to select volumes as claimed in the instant application. Hence the instant claims are not *prima facie* obvious over the combination of cited references. Furthermore, combination of teachings of the cited references does not teach or suggest the unexpected improvement in the **uniformity and reproducibility of the mass spectra** resulting from analysis of samples deposited in such small volumes.

The DECLARATION was provided to show unexpected results, which are results that are not taught or suggested by the cited art. The combination of references does not teach or suggest the unexpected results that derive from using arrays produced by dispensing nanoliter volumes of sample *for mass spectrometric analyses*. The DECLARATION shows that when small volumes as described in the instant application **and as claimed** are dispensed in arrays, the resulting mass spectra resulting from such deposition is uniform (see, *e.g.*, Figure 2 of the attached Exhibit, Little *et al.*) are uniform. They are far more uniform than spectra produced using arrays with larger spots.

As shown in the DECLARATION and the attached exhibit and in the application, when larger sample sizes (*e.g.*, 300 nL), such as the microliter volumes used by Patterson (see, *e.g.*, col. 11, line 56), there is dramatic variability of analyte incorporation and ion yield. This results in the necessity to manually search within the resulting 1 to 2 mm diameter spots for regions from which intense signals can be obtained. This renders such arrays unamenable to automation, and also results in non-uniform spectra. The variability in resulting spectra is too great for such arrays to be used in high throughput applications, such as DNA diagnostics that require automated handling and high

reproducibility. Tisone does not teach or suggest anything about spot size; Tisone is directed solely to a dispensing apparatus.

With the smaller spots that result from the methods and systems as claimed herein, the arrays produced by dispensing small nanoliter volumes result in uniform spectra, and, hence are suitable for use in applications requiring high reproducibility.

Use of arrays of small spots as in the instantly claimed methods results in **improvements, discussed below and in the DECLARATION, in the mass spectrometric analyses that are not taught or suggested by the cited references singly or in any combination thereof.** Therefore the results achieved are by definition unexpected. It is for this purpose that the DECLARATION is provided.

The Examiner states that:

> the declaration and review article specify improved results in mass spectrometric analysis by forming an array from about 300 picoLiter drops, wherein 15 - 20 drops are dispensed into each array element, forming 4.5-6 nanoLiter volume array elements. The specific use of picoLiter droplets provides for rapid evaporation and crystallization of the sample to be detected. The declaration and review article indicate that the mass spectrometric analysis of these arrays is improved over the prior art, which teaches hundred nanoLiter volume array elements. This argument is not germane to the issue since applicant has not restricted that claims to anything but nanoLiter volume array elements, which appears to read on the prior art.

It is noted that neither the presently pending claims nor the claims prior to amendment "read on the prior art." The rejection at issue is a rejection under 35 U.S.C. §103, not 35 U.S.C. §102. As such, the claims "do not read on the prior art" since the art does not teach the elements as claimed. Notwithstanding this, in the interest of advancing prosecution of claims to allowance, the claims (except for claim 5, discussed below) are amended to recite that the volumes dispensed are in the sub to low nanoliter volume range, thereby obviating this objection to the DECLARATION. There is no overlap in volumes dispensed between the instant claims and any cited reference.

The Examiner continues and states that:

> Applicants argue that Tisone does not teach or suggest, of all possible available technologies, which type of analytical technology can be used to analyze the sample transferred by the aspirating operation. Applicants further argue that Tisone does not teach that such a sample can be analyzed by mass spectrometry. The arguments are not persuasive. Firstly, the teaching of all available technologies is irrelevant to the issue because the claimed dispensing methods are clearly taught by Tisone. Secondly, Patterson which the Examiner relies on teaches the mass spectrometry.

Tisone is only directed to a dispensing apparatus and provides no suggestion regarding analysis of dispensed material, and certainly provides no suggestion for methods for preparing and analyzing arrays of very small sample spots by mass spectrometry. Patterson teaches use of microliter volumes. Neither reference teaches or suggests combining the instantly claimed range of volumes dispensed with mass spectrometric analysis.

The Examiner continues:

> With respect to the Patterson reference, Applicants contend that Patterson does not teach combining mass spectrometric analysis with arrays of samples produced by dispensing a nanovolume, nor that it is advantageous to perform mass spectrometry on an array of samples of a size that results from dispensing nanoLiter volumes of material on a substrate. In response to Applicants arguments against the reference individually, one cannot show non obviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091 231 USPQ 375 (Fed. Cir. 1986).

It is respectfully submitted that it is the combination of cited references that the instant Applicant is attacking, not the references individually. In order to show that a *prima facie* case of obviousness has not been set forth, it is first necessary to show the deficiencies in each reference and then show that the combination of teachings when are still deficient. In this instance, the combination of teachings of Patterson and Tisone (or Ershow) does not teach or suggest the results achieved by selection of the range of volumes as claimed herein.

The Examiner continues:

> Applicant further argues that the combination of teachings of the cited references do not teach or suggest the unexpected results that derive from using arrays produced by dispensing nanoLiter volumes of samples for mass spectrometric analysis. This argument is not persuasive because the claimed use of a nanoLiter volume of sample is clearly taught by Tisone.

This is incorrect. Tisone does not suggest selection of low volumes compared to higher volumes and does not teach or suggest the instantly claimed range of volumes. It is not relevant that among the volumes dispensed are 100 nL samples; Tisone (nor Patterson nor Tisone in view of Patterson) does not suggest **selection of** that particular volume for use in mass spectrometric analyses as required by the instant claims. Patterson suggests microliter volumes, and Tisone suggests a variety of volumes. Neither suggests substituting small volumes for the microliter volumes in the mass spectrometric analyses of Patterson.

Finally, the Examiner states:

> Further, one of ordinary skill in the art would recognize that such a low volume of sample dispensing offers several advantages such as, dispensed volume accuracy and uniformity, as well as elimination of wasting expensive samples or reagents, etc.

No basis for this assertion is provided nor does this address the failure of the combination of references to teach or suggest the results achieve by selection of low volumes (sub to low nanoliter volumes) for analysis.

The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The above-noted properties stated by the Examiner as being known, are not "capable of instant and unquestionable demonstration as being "well-known" in the art.

MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

If this position is maintained the Examiner must provide a reference supporting this position.

Second, and more significantly, the DECLARATION is not being provided to show "low volume sample dispensing offers several advantages such as dispensed volume accuracy and uniformity, as well as elimination of wasting expensive samples or reagents". Rather the DECLARATION is provided to show that mass spectrometric analyses that are performed on arrays that result from deposition of small volumes are more uniform and spot-to-spot reproducibility from microdispensed samples is superior to that achieved using samples prepared by conventional pipetting, such as that used by Patterson. The DECLARATION demonstrates that the sample array formed by nanoliter volume dispensing methods having the above-described properties contributes to the shortened spectrum acquisition time (Declaration, paragraph 9), increased detection sensitivity (Declaration, paragraph 10) and makes sample handling far more routine and amenable to automation (Declaration, paragraph 11). When the miniaturized sample dispensing methods were used in dispensing biological samples, *e.g.*, dispensing samples generated in a temperature-cycled PROBE reaction, highly sensitive and accurate analysis could be achieved.

As a result the preparation of arrays of samples for mass spectrometric analysis, as taught in the present specification, permits highly accurate and reproducible mass spectrometric analyses to be performed. By virtue of the small spot size, there is a resulting high sample-to-sample uniformity of the

sample spots, which can be entirely covered by the laser irradiation profile. This eliminates difficulties associated with nonuniform analyte incorporation and translates to a high spectrum acquisition spectrum reproducibility and high speed spectrum acquisition.

These results are not taught or suggested by any of Ershow *et al.*, Patterson *et al.* or Tisone singly or in any combination thereof. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

Claim 5

Claim 5 is amended by incorporation of the limitations of base claims. Claim 5 is directed to the method of dispensing nanoliter volumes of sample and analyzing the resulting arrays by mass spectrometry. Claim 5 further recites that the is achieved by first depositing matrix material on the support, allowing the solvent to evaporate, and then analyte is added to the evaporated matrix material at each locus of the array to dissolve into the matrix material and to form a crystalline structure on at each locus of the substrate surface.

In addition to the reasons of record discussed above, and below, it is respectfully submitted that none of the cited references singly or in any combination thereof, teaches or suggests adding matrix to a surface, permitting the solvent to evaporate and then adding analyte to the matrix to form a crystalline structure.

Analysis

The Claims

Claims 1-4, 6, 9-34, 40-51, 54-69 and 87-94 are directed to methods for forming an array of a sample material on surface of a substrate. The methods include the steps of: providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material; disposing said vesicle adjacent to a first location of surface of a substrate without contacting the surface with the vesicle; providing mechanical pressure to the interior of the vesicle to eject from said chamber a sub to low nanoliter volume

of the fluid to dispense said fluid at said first location of said surface of the substrate; moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a nanoliter volume of fluid is dispensed at each location of said set forming an array of sample material on the substrate; **and performing mass spectrometric analysis of each sample.**

Thus the method includes the step of providing mechanical pressure to the interior of the vesicle to eject from said chamber a nanoliter volume of the fluid to dispense said fluid at said first location of said surface of the substrate.

Dependent claims specify the material that is deposited, the types of vesicle and means for applying pressure, and additional method steps. For example, dependent claim 3 recites that the sample comprises a matrix material for mass spectrometry; claim 4 specifies that method further includes the step permitting the sample with matrix material is dried onto the surface; claim 5 recites that the method of claim 4 further includes adding analyte to the dried matrix to form a crystalline structure on the substrate surface. Dependent claim 6 recites that the sample comprises a matrix material for mass spectrometry and analyte.

Claims 25-30 are directed to methods for analyzing a material by mass spectrometry by dispensing sub to low nanoliter volumes of fluid onto surface of a substrate using the steps of: providing a vesicle comprising a fluid containing the material in a solvent; disposing the vesicle adjacent to a first location of surface of a substrate without contacting the surface with the vesicle; delivering a defined and controlled sub to low nanoliter volume of the fluid at the first location of the surface of the substrate; moving the vesicle to a second position next to the first location on the surface of the substrate to dispense a defined and controlled volume of the material along an array of locations on the substrate surface to form an array of the material; and performing mass spectrometry analysis for the material at each location of the array.

Claims 31-34 are directed to the systems for forming an array of a sample material on surface of a substrate and for analyzing the array of sample material. The systems include a vesicle having a distal end suitable for carrying a nanoliter of fluid; a movable arm having a distal portion mounted to move the vesicle; a controller for moving the arm to dispose the vesicle adjacent to a first location on the surface of the substrate and for controlling the vesicle to provide a sub to low nanoliter volume of the fluid at the first location of the surface of the substrate; and a mass spectrometer for analyzing the material deposited on the surface of the substrate by generating a composition signal representative of the chemical composition of the material.

Claims 40-51 and 54-69 are directed to methods for dispensing nanoliter volumes of a material as an array onto the surface of a substrate, comprising the steps of: (a) providing an assembly having a plurality of vesicles arranged in the form of array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material; (b) aligning the vesicles at a first set of locations adjacent to surface of a substrate without contacting the surface with the vesicle; (c) using mechanical pressure, controlling each of the chambers to eject a sub to low nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles; and (d) providing the resulting substrate with the array of material deposited thereon to mass spectrometer for determining information representative of the composition of the deposited material.

As with the other independent claims dependent claims specify the composition of the material that is deposited, the types of vesicle and means for applying pressure, and additional method steps.

Claims 91-94, specify that the mass spectrometry format used in the methods of claims 31, 40 and 70 is MALDI wherein the mass spectrometry format is matrix assisted laser desorption ionization mass spectrometry.

Th Offic Action fails to s t forth a cas of *prima facie* bviousn ss

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The teachings of the cited references and differences from the claimed subject matter

It is respectfully submitted that Tisone and Patterson, whether alone or in combination, do not render the claimed subject matter prima facie obvious for the reasons set forth in the previous responses and for the reasons discussed

above. As noted, the DECLARATION of record in this application provides results of mass spectrometric analyses performed on arrays of material deposited in accord with methods provided herein and compared to arrays produced with larger volumes. The comparison is provided to show the improvement.

Tisone

Tisone teaches a reagent dispensing apparatus including a positive displacement syringe pump in series with a solenoid valve dispenser. The pump is controlled by a stepper motor to provide an incremental quantity or continuous flow of reagent to the solenoid valve dispenser. The solenoid valve is opened and closed at a predetermined frequency and duty cycle to dispense droplets of reagent onto a target substrate at the metered flow rate.

Tisone also teaches that its apparatus can be used for aspirating ("sucking") precise quantities of reagent or other liquids from a sample or reservoir. At column 11, lines 17-21, Tisone states:

> This mode may be used, for example, in a "suck and spit" operation whereby a precise quantity of fluid is aspirated from one vial containing a sample fluid and then dispensed into another vial or onto a diagnostic test strip for testing or further processing.

Tisone does not teach or even suggest, of all possible available technologies, which type of analytical technology can be used to analyze the sample transferred by the aspirating operation. Tisone certainly does not teach or even suggest that such sample can be analyzed by mass spectrometry, nor that improved performance can be achieved use of arrays produced by dispensing nanoliter volumes. Tisone does not suggest selection deposition of sub to low nanoiter volumes nor, as discussed, show results that derive from such selection.

Patt rson

Patterson does not cure this deficiency. Patterson teaches integrated methods and apparatus for sequencing or identifying polymers by mass spectrometry with a statistical certainty. The methods involve integrating data obtained by mass spectrometry analysis of a series of polymer fragments and statistically comparing the data with hypothetical data corresponding to known sequences or identities. The statistical certainty does not derive from the format subjected to mass spectrometry, but from the algorithms and methodology used to analyze the data. Patterson uses microliter volume samples (not nanoliter volumes as inadvertently typed in the previous response) for analyses (see, col. 11, line 56, - col. 12, line 8).

Patterson does not teach or suggest combining mass spectrometry analysis with arrays of samples produced by dispensing a nanovolumes, particular sub to low nanoliter volumes. Patterson does not teach or suggest that it is advantageous to perform mass spectrometry on an array of samples of a size that results from dispensing a such sub and low nanoliter volumes of material on a substrate. Hence, Patterson does not cure the deficiencies in the teachings of Tisone. The combination of references fails to teach or suggest the instantly claimed methods and systems nor the results achieved thereby

The combination of teachings of the cited references does not result in the instantly claimed methods and systems.

Patterson teaches mass spectrometry of microliter volumes, and Tisone teaches an apparatus for dispensing small volumes of materials. The combination fails to teach or suggest selection of sub to low nanoliter volumes for dispensing for analysis by mass spectrometry. Patterson teaches using microliter volumes and Tisone does not suggest a preference for any particular volume or range thereof. Therefore, the combination of teachings of the cited references does not result in the instantly claimed methods and systems.

With respect to claim 5, as discussed above, the combination of references fails to suggest dispensing matrix, allowing it to evaporate and then adding analyte which dissolves into the matrix to form a crystalline structure.

Unexpected properties

It is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole.

The presently claimed methods and systems possess unexpected properties not taught or suggested by the cited references

THE DECLARATION OF KÖSTER

As discussed above, the unexpected properties of the presently claimed methods are demonstrated in the DECLARATION of Köster pursuant to 37 C.F.R. §1.132. Dr. Köster and his colleagues conducted the experiments presented in the DECLARATION and in the paper Little *et al.*, which is attached to and part of the DECLARATION, as well as in examples in the application.

The results show that the sample array formed by the nanoliter dispensing methods as claimed herein has properties that are not taught or suggested by the cited references. Neither Tisone nor Patterson (nor Ershow), singly or in any combination thereof, teaches or suggests the results achieved when mass spectrometry is performed on an array with drops resulting from deposition of nanoliter-sized volumes.

The DECLARATION shows that spot-to-spot **reproducibility** from microdispensed samples is superior to that achieved using samples prepared by conventional pipetting, such as that used by Patterson. The DECLARATION demonstrates that the sample array formed by nanoliter volume dispensing methods having the above-described properties contributes to the shortened spectrum acquisition time (Declaration, paragraph 9), increased detection sensitivity (Declaration, paragraph 10) and makes sample handling far more routine and amenable to automation (Declaration, paragraph 11). When the

miniaturized sample dispensing methods were used in dispensing biological samples, *e.g.*, dispensing samples generated in a temperature-cycled PROBE reaction, highly sensitive and accurate analysis could be achieved.

As a result the preparation of arrays of samples for mass spectrometric analysis, as taught in the present specification, permits highly accurate and reproducible mass spectrometric analyses to be performed. By virtue of the small spot size, there is a resulting high sample-to-sample uniformity of the sample spots, which can be entirely covered by the laser irradiation profile. This eliminates difficulties associated with nonuniform analyte incorporation and translates to a high spectrum acquisition spectrum reproducibility and high speed spectrum acquisition.

None of the cited reference singly or in combination teaches or suggests that small spot size is desirable for mass spectrometric analyses, nor that the result of such spot size leads to increased reproducibility in the results such that arrays of such spots can be used for analyses. Absent such reproducibility, arrays of samples would not be a suitable for mass spectrometric analyses, such as high throughput DNA diagnostics and sequencing.

Therefore, the presently claimed methods and systems achieve results *i.e.*, the shortened spectrum acquisition time, increased detection sensitivity, greater reproducibility, routine sample handling and amenability to automation that are not taught or suggested by the cited references.

The rejection of claims 70-86 and 94

Claims 70-86 and 94 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ershow *et al.*, which teaches a tool for dispensing small volumes, in view of Patterson, which teaches method for sequencing using a mass spectrometer. The Examiner urges that use of a mass spectrometer to analyze an array of drops, presumably prepared using the dispensing tool of Ershow *et al.* would have been conventional in the art, and hence obvious.

This rejection is respectfully traversed. As discussed in the previous responses and above, the combination of cited references does not render the instantly claimed methods *prima facie* obvious. Notwithstanding this, the DECLARATION of Köster demonstrates results that are not taught or suggested the Ershow *et al.* or Patterson nor any combination thereof. Therefore, any *prima facie* showing of obviousness is rebutted. As above, the DECLARATION demonstrates that results are achieved when an array of spots resulting from deposition of small sized drops is used in mass spectrometric analyses.

Claims

Claims 70-86 and 94 are directed to methods for dispensing nanoliter volumes of a material as an array on the surface of a substrate and analyzing the material in the array by mass spectrometry, comprising the steps of: comprising the steps of: (a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid; (b) loading a nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly; (c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to surface of a substrate without contacting the surface with the vesicle; (d) dispensing a sub to low nanoliter volume of fluid without contacting the loaded fluid to the surface of the substrate aligned with the vesicles, whereby an array of material on the surface of the substrate is formed; and (e) analyzing the resulting arrays by mass spectrometry.

It is acknowledged that Ershow *et al.* does not teach or suggest the step of performing mass spectrometry analysis for the material. Nevertheless, it is alleged that such an analysis step is considered conventional in the art and taught in Patterson. Based on the above teachings, it is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the method of Ershow *et al.* with a mass

spectrometer as taught by Patterson to provide a rapid, automated and cost effective sequencing of polymers with a statistical certainty.

The rejection is respectfully traversed insofar as it applies to any of claims 72-75, 77-78 and 81-83.

Teachings of the cited references

The teachings of Ershow *et al.* and Patterson are discussed as above. As noted above, the statistical certainty alleged to be achieved by Patterson does not derive from the format subjected to mass spectrometry, but from the algorithms and methodology used to analyze the data. Ershow *et al.* does not teach or suggest selection of sub to low nanoliter volumes of material for deposition onto a surface.

Analysis

It is respectfully submitted that Ershow *et al.* and Patterson, whether alone or in combination, do not render the claimed subject matter prima facie obvious. Neither reference singly or in combination teaches selection of the claimed volume range nor the unexpected results achieved when arrays produced by dispensing nanoliter volumes are used in mass spectrometric analysis.

As discussed above and shown in the application, and the attached DECLARATION, the use of such arrays in mass spectrometric analyses results in decreased spectrum acquisition times, permits automation of the processes, and results in highly uniform and reproducible spectra. Such results are not taught or suggested in the cited references. The high reproducibility achieved using the instantly claimed methods does not derive from the paradigm used to analyze the data as in Patterson, but from the format in which the mass spectrometry analyses are performed. Therefore, the claimed subject matter is not prima facie obvious over Ershow *et al.* and Patterson, singly or in any combination thereof.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: LITTLE et al.

Serial No.: 08/786,988

Filed: January 23, 1997

For: SYSTEMS AND METHODS FOR PREPARING AND ANALYZING LOW VOLUME ANALYTE ARRAY ELEMENTS

Art Unit: 1743

Examiner: Bex, P.

ATTACHMENT TO AMENDMENT
MARKED UP CLAIMS (37 C.F.R. § 1.121)

IN THE CLAIMS:

Please amend claims 1, 5, 25, 31, 40 and 70 as follows:

1. (Twice Amended) A method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing the sample material;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a sub to low nanoliter volume of the fluid to dispense said fluid at said first location of said surface of the substrate;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a sub to low nanoliter volume of fluid is dispensed at each location of said set forming an array of sample material on the substrate; and

performing mass spectrometry analysis of the sample material at each location of the array.

5. (Twice Amended) A method for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the resulting array, comprising:

providing a vesicle that has an interior chamber containing a fluid comprising a solvent containing material for deposition;

disposing said vesicle adjacent to a first location on said surface of the substrate without contacting the surface with the vesicle;

providing mechanical pressure to the interior of the vesicle to eject from said chamber a nanoliter volume of the fluid to dispense solvent containing matrix material at said first location of said surface of the substrate, wherein the matrix material is for matrix-assisted laser desorption mass spectrometry;

[The method of claim 3, including the further step of] waiting a predetermined period of time to allow the solvent containing the matrix material to evaporate on the surface of the substrate thereby depositing the matrix material on the surface;

moving said vesicle to each of a set of positions adjacent to the surface of the substrate, whereby a nanoliter volume of fluid is dispensed at each location of said set forming an array of matrix material on the substrate; and

[A method of claim 4, further comprising] ejecting a nanoliter volume of fluid containing an analyte material onto said evaporated matrix material at each locus of the array to dissolve with said matrix material and to form a crystalline structure on [said] at each locus of the substrate surface;

performing mass spectrometry analysis of the sample material at each location of the array.

25. (Thrice Amended) A method for analyzing a material, comprising:

providing a vesicle comprising a fluid containing the material in a solvent;

disposing said vesicle adjacent to a first location of a surface of a substrate without contacting the surface with the vesicle;

delivering a defined and controlled sub to low nanoliter volume of the fluid at the first location of said surface of the substrate;

moving said vesicle to a second position next to the first location on said surface of the substrate to dispense a defined and controlled sub to low nanoliter volume of said material along an array of locations on said substrate surface to form an array of the material; and

performing mass spectrometry analysis for said material at each location of said array.

31. (Thrice Amended) A system for forming an array of a sample material on a surface of a substrate and analyzing the sample material in the array, comprising:

a vesicle having a distal end suitable for carrying a nanoliter of fluid;

a movable arm having a distal portion mounted to move said vesicle;

a controller for moving said arm to dispose said vesicle adjacent to a first location on said surface of the substrate and for controlling said vesicle to provide a sub to low nanoliter volume of the fluid at said first location of said surface of the substrate; and

a mass spectrometer for analyzing said material deposited on said surface of said substrate.

40. (Twice Amended) A method for dispensing sub to low nanoliter volumes of a material as an array onto the surface of a substrate, comprising the steps of:

(a) providing an assembly having a plurality of vesicles arranged in the form of array for dispensing a liquid therefrom, wherein each vesicle has an interior chamber containing a fluid containing the material;

(b) aligning the vesicles at a first set of locations adjacent to the surface of the substrate without contacting the surface with the vesicles;

(c) using mechanical pressure, controlling each of the chambers to eject a sub to low nanoliter volume of the fluid from each vesicle onto the surface of the substrate aligned with the vesicles, whereby an array of the fluid is deposited on the surface of the substrate;

(d) providing the resulting substrate with the array of material deposited thereon to a mass spectrometer for determining information representative of the composition of the deposited material.

70. (Twice Amended) A method for dispensing nanoliter volumes of a material as an array on the surface of a substrate and analyzing the material in the array, comprising the steps of:

(a) providing a pin assembly having a plurality of elongated vesicles arranged as an array for dispensing a liquid therefrom, wherein each vesicle comprises a solid shaft of material having an end for retaining a nanoliter volume of fluid;

(b) loading a nanoliter volume of fluid comprising a liquid material from a fluid source onto the end of the vesicles of the pin assembly;

(c) disposing the pin assembly to align the vesicles at a first set of locations adjacent to a surface of the substrate without contacting the surface with the vesicles;

(d) contacting the loaded fluid to the surface of the substrate aligned with the vesicles <u>to deposit a sub to low nanoliter volume at each location</u>, whereby an array of material on the surface of the substrate is formed; and

(e) analyzing the array of material on the surface of the substrate by mass spectrometry.